Bachelor of Science in Medicine Degree Program
End of Term Final Report

Student Name: Kevin Li **Date:** 08/02/18

Project Title: Epidemiology of Lower Limb Disease In Persons with Chronic Kidney Disease

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Summary (250 words max single spaced):

Lower limb complications (foot ulcers and lower limb amputations) are major problems commonly seen in patients with peripheral vascular disease (PVD) and chronic kidney disease (CKD). Lower limb complications are a significant cause of suffering and reduced quality of life. The association between CKD and development of lower limb complications has been well studied, however, the opposite is not true. We sought to determine how interim lower limb complications modify the subsequent risk of progression to kidney failure, all-cause mortality prior to kidney failure and cardiovascular events in a cohort of stage 3-5 CKD patients.

We performed a retrospective cohort study of 92,618 individuals using patient level data obtained by linking several administrative databases from Manitoba, Canada. The rate of kidney failure, all-cause mortality prior to kidney failure and cardiovascular related hospitalization were significantly higher in persons experiencing an interim lower limb complication. After adjusting for baseline characteristics and co-morbidities, experiencing an interim lower limb complication increased the risk of progressing to kidney failure, all-cause mortality and cardiovascular related hospitalization by more than 2-fold. Clinical trials of screening and treatment strategies for CKD patients experiencing lower limb complications is urgently needed.

Student Signature

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Introduction

Chronic kidney disease (CKD) is an emerging public health problem worldwide with increasing incidence and prevalence rates[1,2]. This rise is likely to continue due to the increasing age of the population as well as increased rates of diabetes mellitus (DM), a major risk factor for the progression of CKD[3,4]. CKD can progress to kidney failure which is costly, and can lead to significant morbidity and mortality. Patients with CKD and diabetes are at high risk of microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (peripheral vascular disease, ischemic heart disease, cerebrovascular disease)[5,6]. In particular, peripheral vascular disease (PVD) is a common macrovascular complication that carries considerable morbidity in patients with CKD[6,7]. CKD patients are more likely to develop PVD compared to the general population[6,7]. Mechanisms of PVD involves pathologic narrowing and occlusion of vasculature in the extremities due to ongoing arteriolosclerosis and thrombosis[9].

Lower limb complications (foot ulcers and lower limb amputations) are a major problem frequently seen in patients with PVD and CKD. Multiple risk factors including diabetes, peripheral neuropathy, vascular insufficiency, structural deformities and CKD progression, contribute to the risk of developing lower limb complications[3,10]. Lower limb complications are a significant cause of suffering and reduced quality of life. Recurrence of foot ulcers in CKD patients with PVD is over 50% within 3 years of initial healing[11]. This high recurrence rate can be explained by reduced blood flow from PVD, immune compromise from CKD and overall lack of protective sensations from neuropathy. Progression of lower limb complications may reach a point of limb amputation which significantly impacts patient quality of life, increases mortality risk and healthcare costs[11,12]. Patients with end-stage renal disease receiving dialysis have a 10-fold higher incidence of lower limb amputation compared to the general diabetic population[13]. Some studies have shown as much as 66.6% of patients with kidney failure receiving dialysis die within 2 years following their first lower limb amputation[3]. This illustrates the severity of risk lower limb complications pose for patients with PVD and CKD.

Over the past decade, multiple studies have shown the association between CKD and PVD, and demonstrated the graded risk of PVD with the transition from CKD to dialysis[7,13,14]. CKD with progression to kidney failure has been identified as a risk factor for the development of diabetic foot ulceration and lower limb amputations. Other studies have shown patients with DM receiving dialysis are at higher risk of developing lower limb complications compared to DM alone or patients receiving dialysis without DM[3,5]. The majority of studies have focused on the relationship of CKD and kidney failure and the effect on lower limb complications[7,13,14], however, gaps in knowledge still exist about how lower limb complications from PVD affect CKD progression. The aim of this study is to determine how a cohort of patients with stage 3-5 CKD experiencing lower limb complications (foot ulcer or foot amputation) modify their subsequent risk of progression to kidney failure, all-cause mortality prior to kidney failure and cardiovascular related hospitalization.

Materials and Methods

Study Design

We performed a retrospective cohort study analyzing patient level data obtained by linking several administrative databases housed at the Manitoba Centre for Health Policy (MCHP) in Manitoba, Canada, an organization that has for the past 25 years housed and integrated several administrative databases related to social and health services provided to Manitoba residents[16]. Included databases were the Manitoba Health Insurance Registry (patient demographics and follow-up information), the Discharge Abstract Database (hospital admissions), Medical Services (physician claims), Vital Statistics (cause-specific mortality), and Diagnostic Services of Manitoba (laboratory results). The study protocol was reviewed and approved by the University of Manitoba Health Research Ethics Board (HS18574). All data provided was de-identified using a scrambled personal health identifier and patient consent was waved.

Study Cohort

We included all adult (age 18+) patients from Manitoba, Canada (population 1.3 million) with Stage 3 or higher CKD using serum creatinine tests from the Diagnostic Services of Manitoba database, taking the first recorded eGFR below 60ml/min/1.73m^2 between January 1st 2007 and October 31st 2014, with the study entry (index date) defined as the date of serum creatinine test. eGFR was calculated using the CKD-EPI study equation[17]. Patients receiving dialysis or with a functioning transplant prior to this first eGFR were excluded.

Outcomes

The primary outcomes of interest in our study included (1) kidney failure adjusted for the outcome of all-cause mortality before kidney failure; (2) death before kidney failure; and (3) cardiovascular-related hospitalization adjusted for the risk of non-cardiovascular death. End stage renal disease was established as the first claim for chronic dialysis or a renal transplant using tariff codes from the Manitoba Physician's Manual[18]. Cardiovascular-related hospitalizations were ascertained using ICD-9 and ICD-10 codes[4] and included either a primary or secondary diagnosis in the Discharge Abstract Databases. Cardiovascular-related mortality was established using the Vital Statistics database with a cause of death attributed to any ICD-10 code starting with I (diseases of the circulatory system).

Exposure Variables of Interest

Baseline characteristics and co-morbidities were ascertained between January 1st 2004 and entry into the study cohort. The primary exposure of interest was an interim lower limb complication, defined as a diabetic foot ulcer or non-traumatic limb amputation. Baseline characteristics included: demographic information (age and sex), laboratory data (eGFR, urine albumin-to-creatinine ratio (ACR), hemoglobin A1C), and comorbid conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease and diabetes).

Statistical Analysis

Descriptive statistics were presented as mean and standard deviation or median and interquartile range for continuous variables and percentages for categorical data. Comparisons

were evaluated between individuals who had an interim lower limb complication (between study entry and the outcome of mortality or kidney failure) and those who did not using the appropriate statistical test (e.g. t-test, Wilcoxon rank sum test, and the chi-square test). We developed Cox proportional hazards models to evaluate the aforementioned outcomes. Models included (1) a Fine and Gray competing risk model with the outcome of kidney failure and the competing risk of all-cause mortality; (2) a proportional hazards model with the outcome of all-cause mortality before kidney failure; and (3) a Fine and Gray competing risk model with the outcome of a cardiovascular hospitalization and the competing risk of non-cardiovascular death. Our primary exposure variable was the first interim lower limb complication modeled as a time-dependent covariate. Models were adjusted for baseline demographics (age, sex) and co-morbid conditions myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease and diabetes). Assessment of proportionality was performed by visual inspection of scaled Schoenfeld residuals plotted over time. Multi-collinearity was assessed using a linear regression model and evaluating variance inflation factors (VIFs). All statistical analysis was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC) and we used a 2-sided significance level of $P < 0.05$.

Results

Cohort Selection

The DSM database housed chemistry data for approximately 3,962,421 individuals with at least one serum creatinine measurement during our study period from January 1st 2007 to October 31st 2014. We were able to calculate an eGFR on 3,955,116 individuals, of which 95,344 unique individuals had a eGFR $\leq$ 60ml/min/1.73m^2. 1,380 individuals with functioning renal transplants or those receiving dialysis treatment at baseline were excluded. 797 individuals died on the same day that their first measured eGFR fell below 60ml/min/1.73m^2 and were not included in the cohort. An additional 549 individuals were excluded due to invalid registration. This yielded a final cohort of 92,618 individuals with stage 3 to 5 CKD. The study population is summarized in Figure 1.

Population Characteristics

Of these 92,618 individuals with stage 3 to 5 CKD, the mean age was 72 years and mean eGFR was 46.5ml/min/1.73m^2 (Table 1). At the time of referral 11.96% of individuals had previous myocardial infarction, 23.4% had congestive heart failure, 13.4% had peripheral vascular disease, 17.7% had cerebrovascular disease, 36.4% had chronic pulmonary disease and 33.8% had diabetes at baseline.

Individuals with interim lower limb complications were younger (68 years compared to 72 years) and a greater proportion were male (60%). eGFR in these individuals was lower (43.9ml/min/1.73m^2) while urine ACR was higher (91.3mg/g). The prevalence of comorbid conditions was higher in those with interim lower limb complications compared to those that did not experience interim lower limb complications (Table 1). This burden was especially worrisome in individuals with comorbid diabetes, peripheral vascular disease and congestive heart failure. Prior lower limb complications, amputation and diabetic foot ulcers were significantly more prevalent in individuals experiencing interim lower limb events compared to those without interim lower limb events.

Outcomes in Patients With and Without Interim Lower Limb Complications

The incidence of kidney failure before all-cause mortality was highest in those experiencing interim lower limb complications at 11% while the incidence was only 3% in the total population as well as individuals that did not have an interim lower limb event. Similarly, those experiencing interim lower limb complications had a higher incidence of all-cause mortality before kidney failure (52% vs 35%) and CV related hospitalization (31% vs 21%) when compared to all patients and those that did not have an interim lower limb complication.

Kidney failure competing with all-cause mortality: Unadjusted rates for kidney failure before all-cause mortality were 1.0 per 100 person years in patients that did not experience an interim lower limb complication. In contrast, unadjusted rates for kidney failure before all-cause mortality in patients that did experience an interim lower limb complication was 3.1 per 100 person years. After adjusting for age, sex, eGFR and comorbidities, individuals experiencing interim lower limb complications had a 2.5-fold higher risk of progressing to kidney failure when compared to those that did not have an interim lower limb complication.

All-cause mortality prior to Kidney failure: Unadjusted rates for all-cause mortality prior to kidney failure was 11.9 per 100 person years and 14.5 per 100 person years for those that did not and those that did experience an interim lower limb complication, respectively. There was a 2.7-fold increased risk of all-cause mortality in those that experienced an interim lower limb complication.

CV hospitalization prior to non-CV related death: Unadjusted rates for cardiovascular events prior to non-cardiovascular related death was 7.7 per 100 person years in those that did not experience an interim lower limb complication, while the rate was 21.7 per 100 person years in those that did have an interim lower limb complication. There was a 2.1-fold increased risk of CV related hospitalization for those experiencing interim lower limb complications.

Non-CV related death (not shown on tables): Unadjusted rates for non-CV related death in patients not experiencing interim lower limb complications was 4.95 while those with interim lower limb complications was 3.2.

Discussion

In our province wide population study of 92,618 individuals with stage 3 to 5 CKD, we have found that interim lower limb complications are common in individuals with reduced eGFR. The presence of interim lower limb complications puts patients at higher risk of progressing to kidney failure, all-cause mortality before kidney failure and CV related events, compared to those that did not experience interim lower limb complications. After adjusting for baseline factors and comorbid conditions, we found that an interim lower limb complication was associated with more than 2-fold increased relative risk of subsequent progression to kidney failure, all-cause mortality before kidney failure and CV related hospitalization, respectively. Together, these findings highlight the burden of lower limb complications in the CKD population and suggest early interventions are needed to reduce this risk of disease progression and mortality in this population.

The effect of CKD progression and dialysis treatment on development of lower limb complications (diabetic foot ulcers and lower extremity amputations) has been well studied[5,14,15]. In a cohort study of 90,617 participants with diabetes in The Health Information Network (THIN) from the U.K, investigators examined the association of foot ulcers and lower limb amputations.

Their findings show a strong association between CKD severity and development of diabetic foot ulcers and lower extremity amputations in those with diabetes[15]. This risk was more apparent as CKD became more severe. However, the study population only included individuals with diabetes, making it difficult to apply these findings to patients that only have CKD and not diabetes. In another cohort study of 669 individuals from the Netherlands, investigators examined the incidence of foot ulceration and lower extremity amputation in all individuals with CKD stage 4-5 and individuals receiving dialysis, with CKD stage 3 as the reference for comparison. Their findings show a 4-fold and 8-fold increased risk of foot ulceration in individuals with CKD stage 4-5 and those on dialysis, respectively[14]. This further illustrates the increased risk of lower limb complications as CKD progresses ultimately to kidney failure. Several other studies have examined the relationship between CKD and dialysis treatment and their effect on the risk of developing lower limb complications[5,13,19] all reporting similar conclusions of increased risk as CKD progresses or as dialysis is warranted.

Although many studies have examined the risk of developing lower limb complications as a consequence of CKD and kidney failure, the opposite is not true. To our knowledge, there have not been any studies that examine the association between lower limb complications and the risk of progression to kidney failure in patients with CKD. Furthermore, there is data examining the survival rates of individuals with diabetes following an amputation[13], however, there is currently no data on how lower limb complications modify the risk of all-cause mortality prior to kidney failure. There is also very little published data examining the effect of lower limb complications on the development of cardiovascular events requiring hospitalization. Interestingly, our data suggests in a cohort of patients with stage 3-5 CKD, the presence of a lower limb complication is a stronger risk factor for development of cardiovascular events than myocardial infarction, peripheral vascular disease or cerebrovascular disease.

The results from our population wide study have clinically important implications. The increased risk of subsequent progression to kidney failure, all-cause mortality before kidney failure and CV related hospitalization is relevant to clinicians examining patients with lower limb complications. Clinicians should consider additional monitoring and treating risk factors for lower limb complications. Previous lower limb complications, vascular insufficiency, peripheral neuropathy and skin/nail deformity have been shown to be major risk factors in developing subsequent lower limb complications[10]. These risk factors have been demonstrated to be the same in CKD patients without diabetes, as well as patients who only have diabetes[10]. The importance of early detection and management of these underlying risk factors is imperative to reduce the severe consequences of lower limb complications. The rates of foot salvage in patients with foot ulcers and kidney failure are quite low leading to increased need for amputation[20-23]. Furthermore, progression of foot ulcers to amputations has a significant effect on mortality with one study suggesting as much as 60% of individuals with diabetes die within 5 years of experiencing a lower extremity amputation[24]. Additionally, amputation in people with diabetes has a higher in-hospital and 30-day mortality than in people who undergo coronary artery bypass graft, breast cancer or stroke[25-27]. These severe consequences highlight the need for early recognition and prevention. Fortunately, early interventions including foot care exams, foot care services and management of complications has shown promising results to improve clinical outcomes and prevent hospitalization in patients with diabetes and for those requiring dialysis[28,29]. As our study indicates, the increased risk of kidney failure, all-cause mortality prior to kidney failure and CV related hospitalization following a lower limb complication suggests similar foot care interventions should be considered, not just in diabetes and dialysis populations, but in CKD populations as well.

Our retrospective cohort study has several strengths including the use of a validated set of administration codes with a large sample size that comprised of our population based cohort of patients. The use of a competing risk model for the analysis of our data allowed for a determination of how lower limb complications modify risk of 3 clinically relevant outcomes in CKD patients. Our time-dependent model accounted for baseline and interim lower limb complications while also adjusting for comorbid conditions. There are also limitations to our study. Due to the retrospective nature of our study, all variables were accessed from medical files. Although we used a well validated administrative code set, by design we could not determine disease severity or duration. Additionally, although we accounted for confounders such as diabetes and pre-existing peripheral vascular disease, it is possible that lower limb complications are a marker for poorly controlled diabetes rather than a causal event. We could not examine this limitation through our retrospective design, however, this provides an opportunity for future interventional studies to examine.

Conclusion

Lower limb complications are common in patients with chronic kidney disease. Having a lower limb complication increases the risk of progressing to kidney failure, all-cause mortality prior to kidney failure and CV related hospitalization by more than 2-fold. Clinical trails of screening and treatment strategies for lower limb complications in patients with chronic kidney disease are urgently needed.

TABLES AND FIGURES

Figure 1. Flow Diagram of final cohort selection and entry into the study.

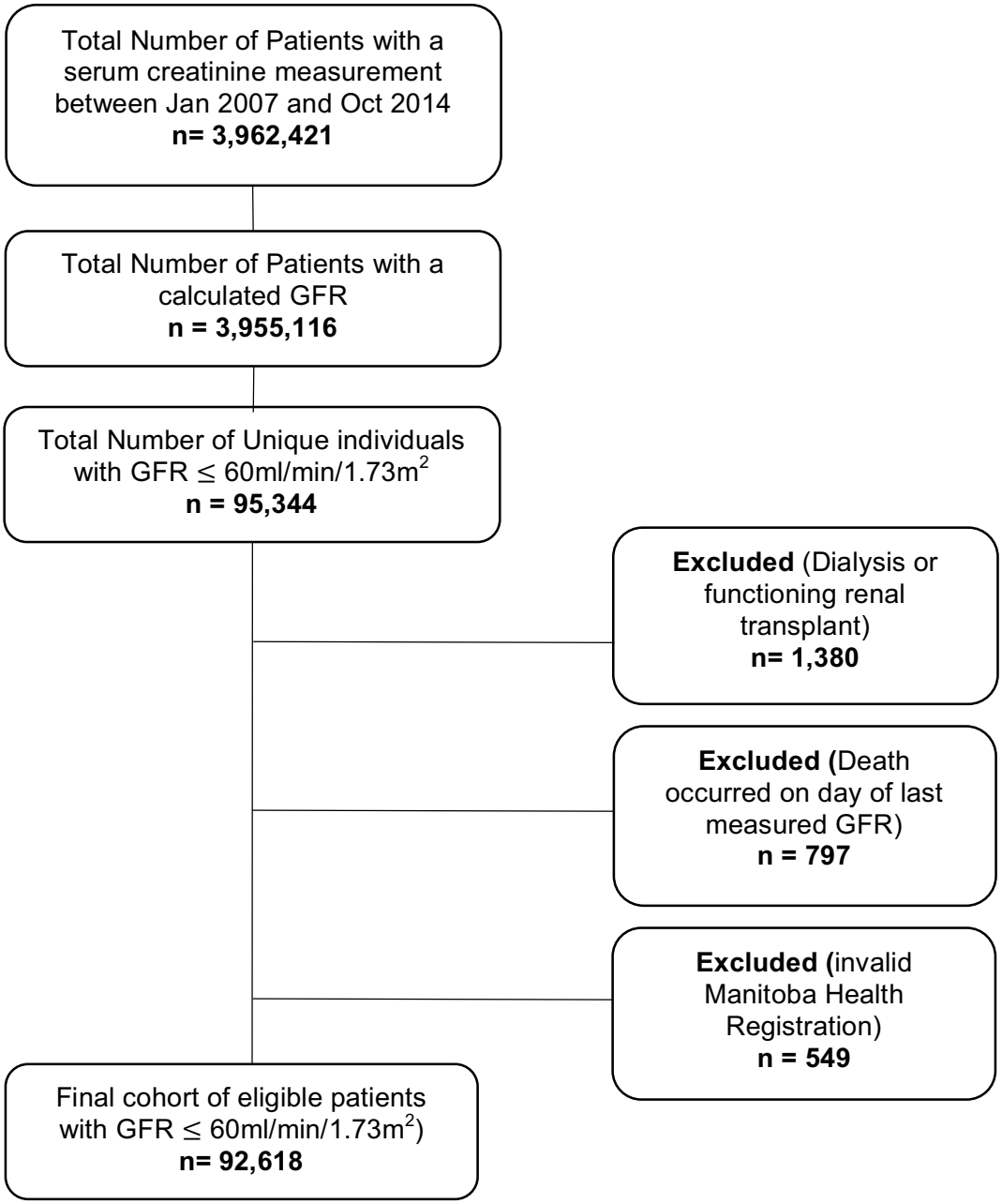

Table 1: Patient baseline characteristics for interim lower limb complications competing risk of kidney failure and all-cause mortality.

	All patients	Interim Lower Limb Complication	No Interim Lower Limb Complication
Population Characteristics			
Total n	92618	1739	90879
Age, mean (SD)	72 (15.8)	68 (13.7)	72 (14.5)
Male sex (%)	42818 (46%)	1045 (60%)	41773 (46%)
Lab Values			
eGFR, mean (SD)	46.5 (12.5)	43.9 (13.3)	46.5 (12.5)
Urine ACR, mean(SD)	38.8 (283) n=18372	91.3 (180) n=686	36.7 (286) n=17686
HbgA1C, mean (SD)	6.98 (1.8) n=31346	8.38 (2.3) n=1255	6.93 (1.7) n=30091
Comorbidities			
Acute MI	11073 (11.96%)	373 (21.45%)	10700 (11.77%)
Congestive Heart Failure	21674 (23.4%)	662 (38%)	21012 (23%)
Peripheral Vascular Disease	12374 (13.4%)	637 (36.6%)	11737 (12.9%)
Cerebrovascular Disease	16367 (17.7%)	373 (21.5%)	15994 (17.6%)
Diabetes	31290 (33.8%)	1436 (82.6%)	29854 (32.9%)
Chronic Pulmonary Disease	33695 (36.4%)	569 (32.7%)	33126 (36.5%)
Baseline Procedures			
Prior Lower Limb Complication	1610 (1.74%)	474 (27%)	1136 (1.25%)
Prior Lower Limb Amputation	753 (0.81%)	216 (12.4%)	537 (0.59%)
Prior Diabetic Foot Ulcer	1287 (1.4%)	418 (24%)	869 (0.96%)

*All percentages were calculated based on the total n in each column.

Table 2: Event rates for the outcomes of interest and a multivariate cox proportional hazards model* stratified by presence of interim lower limb complication.

	Kidney Failure before All-Cause Mortality			All-Cause Mortality before Kidney Failure			CV Hospitalization before Non-CV Related Death		
	Incidence	Event Rate (per 100 person years)	Hazard Ratio (95% CI)	Incidence	Event Rate (per 100 person years)	Hazard Ratio, (95% CI)	Incidence	Event Rate (per 100 person years)	Hazard Ratio (95% CI)
All Patients (n= 92618)	2946 (3%)	1.07	-	32863 (35%)	11.91	-	19717 (21%)	7.98	-
LLC[1] Yes (n = 1739)	195 (11%)	3.16	2.5 (2.1-3)	897 (51.6%)	14.52	2.7 (2.5-2.9)	382 (31%)	21.67	2.1 (1.9-2.4)
LLC[1] No (n = 90879)	2751 (3%)	1.02	-	31966 (35%)	11.85	-	19335 (21%)	7.62	-

[1]LLC = Lower Limb Complication

*Cox proportional hazards model is adjusted for age, sex and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease and diabetes). Confidence intervals with alpha=0.05.

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